SUMMARY OF INVENTION

Technical Problem

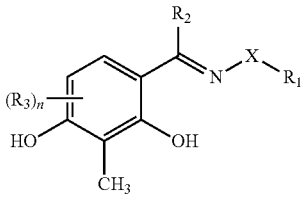
[0026] The present invention aims to provide a novel kinase inhibitor. Particularly, the present invention aims to provide a novel kinase inhibitor that inhibits the Hippo signal transduction pathway. In addition, the present invention also aims to provide a therapeutic agent for a disease, a screening method for drug discovery, and the like that utilize the inhibitor.

Solution to Problem

[0027] The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that a specific compound inhibits the activity of plural protein kinases including LATS (particularly LATS2). In addition, the present inventors found that the specific compound promotes nuclear translocation of an intracellular YAP protein, promotes expression of the target gene group of YAP or TAZ protein, the activity varies greatly depending on the optical isomer in specific compounds having an asymmetric carbon, and the like. Based on such finding, they have conducted further studies and completed the present invention. Therefore, the present invention provides the following.

[1] A kinase inhibitor comprising a compound represented by the following formula (I), or a salt thereof:

I



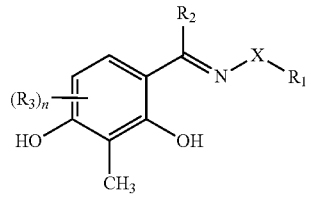
{wherein, X is a single bond, —CH_2COO—, —CONH—, or —NHCO—, R_1 is an alkyl group having 1-10 carbon atoms and optionally having substituent(s), an aryl group optionally having substituent(s), or —Y—W—Z—Ar wherein Y and Z are each a single bond or an alkylene group having 1-6 carbon atoms and optionally having substituent (s), W is an oxygen atom, a sulfur atom or N(R_4), R_4 is a hydrogen atom or an alkyl group having 1-6 carbon atoms, Ar is an aryl group optionally having substituent(s), R_2 is an alkyl group having 1-6 carbon atoms and optionally having substituent(s), R_3 is a hydroxyl group, and n is 0, 1 or 2}.

[2] The inhibitor of [1], wherein the kinase is selected from the group consisting of CGK2, LATS2, MSK1, p70S6K, PKACα, PKACβ, SGK2, and SGK3.

[3] The inhibitor of [2], wherein the kinase is LATS2.

[4] A Hippo signal transduction pathway inhibitor comprising a compound represented by the following formula (I) or a salt thereof:

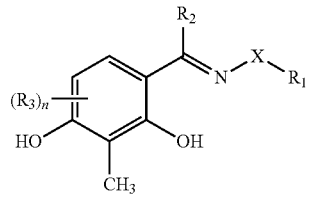
(I)



{wherein, X is a single bond, —CH_2COO—, —CONH—, or —NHCO—, R_1 is an alkyl group having 1-10 carbon atoms and optionally having substituent(s), an aryl group optionally having substituent(s), or —Y—W—Z—Ar wherein Y and Z are each a single bond or an alkylene group having 1-6 carbon atoms and optionally having substituent (s), W is an oxygen atom, a sulfur atom or N(R_4), R_4 is a hydrogen atom or an alkyl group having 1-6 carbon atoms, Ar is an aryl group optionally having substituent(s), R_2 is an alkyl group having 1-6 carbon atoms and optionally having substituent(s), R_3 is a hydroxyl group, and n is 0, 1 or 21.

[5] A therapeutic agent for a disease or tissue damage associated with failure of cellular proliferation, comprising a compound represented by the following formula (I) or a salt thereof:

(I)



{wherein, X is a single bond, —CH_2COO—, —CONH—, or —NHCO—, R_1 is an alkyl group having 1-10 carbon atoms and optionally having substituent(s), an aryl group optionally having substituent(s), or —Y—W—Z—Ar wherein Y and Z are each a single bond or an alkylene group having 1-6 carbon atoms and optionally having substituent (s), W is an oxygen atom, a sulfur atom or N(R_4), R_4 is a hydrogen atom or an alkyl group having 1-6 carbon atoms, Ar is an aryl group optionally having substituent(s), R_2 is an alkyl group having 1-6 carbon atoms and optionally having substituent(s), R_3 is a hydroxyl group, and n is 0, 1 or 2}.

[6] The therapeutic agent of [5], wherein the disease or tissue damage associated with failure of cellular proliferation is a disease associated with suppressed nuclear translocation of YAP and/or TAZ.

[7] The therapeutic agent of [5], wherein the disease or tissue damage associated with failure of cellular proliferation is selected from the group consisting of inflammatory disease, inflammatory bowel disease, neurodegenerative disease, immune-nerve disease, muscular dystrophy, myopathy, trauma, burn, chemical burn, skin ulcer, traumatic ulcer, lower leg ulcer, frostbite ulcer, immune-ulcer, postherpetic ulcer, radiation ulcer, pressure ulcer, diabetic skin ulcer, giant pigmented nevus, scar, disorder due to tattoo, vitiligo vulgaris, leukopathia, spinal cord damage, muscle damage, liver failure, drug-induced hepatopathy, alcohol-induced hepatopathy, ischemic hepatopathy, viral hepatopathy, auto-